REMARKS

The Pending Claims

Claims 1, 4, 6-15, and 18-20 remain pending, claims 1, 4, 6, 7, and 9-15 have been withdrawn from consideration, claims 2, 3, 5, 16, and 17 have been canceled without prejudice, and claims 21-26 are added.

Claims 8 and 18-20 have been amended, and claims 21-26 have been added, to describe the invention more clearly. No new matter has been added, the basis for the amended claim language may be found within the original specification, claims and drawings. Claim 8 is supported at, for example, page 9, line 26, page 13, line 4, and page 17, lines 6-7. Claims 21 and 22 are supported at, for example, page 16, lines 15-25. Claims 23-26 are supported at, for example, page 14, lines 14-17.

The Office Action

For convenience, the following remarks will address the various objections and rejections in the same order they were raised in the Office Action.

Objections

The Office Action objected to the title, abstract, and the specification.

The title, the abstract, and the specification, have been amended. In amending the title and abstract, the word "New" has been deleted. The specification has been amended to correct various misspellings and to improve the grammar.

Claim 8 was objected to as not following parallel sentence construction and for referring to "a" effective amount. The claim has been amended as suggested in the Office Action.

Thus, it is respectfully submitted that with these remarks and amendments to the title, the abstract, the specification, and the claims, the objections have now been overcome and should be withdrawn.

Rejections under 35 USC 112

Claims 2, 3, 5, 8, and 16-20 were rejected under 35 USC 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. According to the Office Action, the phrase "separately" in claim 8 is indefinite in view of a prior phrase in the claim.

Claim 8 has have been amended to replace "a" with --an-- (in referring to "effective amount) as noted above, and to delete the word "separately" improve the form of the claim and more distinctly claim the subject matter which Applicants regard as their invention.

Thus, it is respectfully submitted that with these remarks and amendments to the claim 8, the rejection under 35 USC 112 has now been overcome and should be withdrawn.

Claims 2, 3, 5, 8, and 16-20 were rejected under 35 USC 112, first paragraph, as the Office Action alleges that the specification, while enabling for treating stroke, cerebral infarction, head injury, cerebral hemorrhage, cerebral thrombosis, cerebral embolism, and transient ischemic attacks with the combination of t-PA and FK506, does not reasonably provide enablement for preventing or treating any cerebral neurodegenerative disease in any individual by administering any plasminogen activator and any IL-2 inhibitor. These claims are also rejected under 35 USC 112, first paragraph as Office Action also alleges the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant are that the inventors, at the time the application was filed, had possession of the claimed invention.

These rejections are respectfully traversed.

Claim 8 has been amended to refer to, *inter alia,* "t-PA" and "tacrolimus or its hydrate" and preventing or treating "cerebral ischemic disease and/or brain damage caused by ischemia." The term "neurodegenerative" has been deleted.

Additionally, claim 19 has been amended to, *inter alia,* delete "hypertensive encephalopathy, Alzheimer's disease, Huntington's disease, Parkinson's disease, and amyotrophic lateral sclerosis (ALS)."

Thus, it is respectfully submitted that with these amendments to the claims, the rejections under 35 USC 112 first paragraph have now been overcome and should be withdrawn.

Rejection under 35 USC 103

Claims 2, 3, 5, 8, and 17-20 were rejected under 35 USC 103(a) as being unpatentable over NINDS, 1995 (*N. Engl. J. Med. 333*:1581-1587) in view of Bundick et al, 1992 (*Transplantation, 53*:1150-1153) and Mori et al., 1997 (*J. Immunol.* 158: 659-3665), and further in view of Sharkey et al., 1994 (*Nature, 371*:336-339) or Kelly et al., 1997 (U.S. Pat. No. 5,648,351) as evidenced by Steiner et al., 1998 (*Eur. Neurol., 40*:1-8).

This rejection is respectfully traversed.

Applicants submit that the Office has failed to establish a *prima facie* case of obviousness in regard to the present invention. One of ordinary skill in the art would not be led

to modify the teachings of NINDS in the precise manner which yields the claimed invention. As the Office Action correctly notes, NINDS does not teach combination therapy with t-PA and an IL-2 inhibitor. Accordingly, even if Bundick et al. and Mori et al. each disclose FK506 is an IL-2 inhibitor, and even if Sharkey et al. and Kelley et al. each disclose FK506 has neuroprotective activity, this is of no import. Bundick et al., Mori et al., Sharkey et al., and Kelley et al., whether taken alone or in combination, do not cure the deficiencies of NINDS, and thus, the combination fails to render the present invention obvious.

Moreover, while Steiner et al. refers to combination therapy, there is absolutely no reference to FK506. Additionally, not only does Steiner et al. refers to a "number of problems" (*see*, Abstract) with respect to combination therapy, but, in referring to neuroprotective and cytoprotective drugs, Steiner et al. also indicates "only <u>few</u> have shown positive clinical results" (page 2, right column, second paragraph (emphasis added); *see also*, Table 1, page 4, indicating various trials have been abandoned or terminated). Thus, Steiner et al. merely speculates that combination therapy with thrombolytic and neuroprotective agents "<u>may provide</u> additional benefits" (Abstract, emphasis added) and does not lead one of ordinary skill in the art to administer effective amounts of both t-PA and tacrolimus or its hydrate to a human being or animal.

As described and shown by the inventors, the administration of effective amounts of t-PA and tacrolimus to treat cerebral ischemic disease and/or brain damage caused by ischemia in accordance with the present invention is highly effective. Example 1 (pages 15-17) shows, in treating a thrombotic occlusion of the middle cerebral artery (MCA) in rats, administering FK506 or t-PA 2 hours after occlusion results in little inhibition of brain damage. However, "the combination of FK506 and t-PA caused the significant reduction of ischemic brain damage and its inhibition is more than 23%, which is greater than that of FK506 or t-PA alone" (page 16, lines 17-20).

It is respectfully submitted that this showing of a synergistic effect further evidences the non-obviousness of the claimed invention.

Additionally, the Example shows that while t-PA administered 3 hours after occlusion increased the brain damage (page 16, lines 21-22), "the combination of FK506 and t-PA caused the significant reduction of ischemic brain damage and its inhibition" (page 16, lines 23-24).

Advantageously, administering FK506 and t-PA prolongs the therapeutic time window and also provides increased efficiency and safety for treating ischemic brain damage (page 16, line 28, through page 17, line 2).

Accordingly, since the cited art does not lead one of ordinary skill to the claimed invention, and in view of the synergistic effect and other advantages shown, it is respectfully submitted that the rejection cannot be maintained.

For the reasons set forth above, reconsideration of the rejections is respectfully requested.

Conclusion

In view of the amendment and remarks recited herein, the application is considered in good and proper form for allowance, and the Examiner is respectfully requested to pass this application to issue.

If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

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